

### REMARKS

Claims 23-30, 32, 34, 36, and 39 are pending. Claims 1-22, 31, 33, 35, 37-38 and 40-45 have been cancelled in this Amendment or in prior Amendments. Claims 46-53 have been withdrawn from consideration due to the Examiner's restriction requirement. These claims have been cancelled or withdrawn from consideration without prejudice to, or disclaimer of, the subject matter thereof. Applicant reserves the right to file continuation applications directed to the subject matter of any claim cancelled for any reason. New claims 54-56 are presented for examination. Support for these claims can be found throughout the specification, e.g., at page 17, lines 5-8 and 15-17.

The above amendments and new claims place the application in better condition for examination. It is submitted that no new matter has been introduced by the present amendments and new claims, and entry of the same is respectfully requested. By the amendments and new claims, Applicant does not acquiesce to the propriety of any of the Examiner's prior rejections and does not disclaim any subject matter to which Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

In the specification, page 9, lines 18-19; page 10, lines 22-28; page 22, line 9 - page 23, line 27; page 24, line 1 - page 25, line 26; page 25, line 30 - page 27, line 27; and page 27, line 31 - page 29, line 12 have been amended to correct obvious typographical errors.

### I. OBJECTIONS TO THE SPECIFICATION

The Examiner objected to several aspects of the disclosure of the present application. Office Action mailed 27 January, 2004 ("OA") at pages 2-4. Applicant respectfully traverses.

The Examiner asserted that the Title of the invention is not descriptive. *Id.* at 3. Without acquiescing to the propriety of this objection and solely to expedite prosecution of the present application, the Title has been amended to read, "Methods For Identification Of Identical Nucleic Acid Fragments From Different Nucleic Acid Populations."

The Examiner alleged that the abstract should be provided on a separate sheet of paper and that a claim of priority should be included. *Id.* Applicant has provided the Abstract on a separate sheet of paper and a claim of priority has been added. Based on these changes, Applicant respectfully requests that the Examiner reconsider and withdraw the present objections.

The Examiner required that the use of the trademarks “Quiaex II” and “Z-Taq” be capitalized and accompanied by the appropriate generic terminology. *Id.* Without acquiescing to the propriety of this objection and solely to expedite prosecution of the present application, the reference to “Quiaex II” has been amended to more clearly identify the appropriate generic terminology. Each reference to “Quiaex II” and “Z-Taq” is capitalized in the application and the appropriate generic terminology, gel extraction kit and high fidelity long-range DNA polymerase, respectively, is included. Applicant respectfully requests that the Examiner reconsider and withdraw this objection.

The Examiner objected to claim 35 under 37 C.F.R. 1.75(c) as being in improper dependent form for failing to further limit the subject matter of a previous claim. *Id.* Without acquiescing to the propriety of this objection and solely to expedite prosecution of the present application, the Applicant has cancelled claim 35.

Finally, the Examiner suggested that the term “chosen” be amended to “selected” in claim 36. *Id.* at 4. Without acquiescing to the propriety of this objection and solely to expedite prosecution of the present application, claim 36 has been amended accordingly. Applicant respectfully requests that the Examiner reconsider and withdraw this objection.

Based on the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the objections to the specification.

## **II. REJECTIONS UNDER 35 U.S.C. § 112, ¶ 2**

Claims 23-45 were rejected under 35 U.S.C. § 112, ¶ 2, “as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.” *Id.* at 4. Applicant respectfully traverses.

The Examiner asserted that claims 23-45 are indefinite because claim 23 is drawn to a method for the identification, isolation or separation of “identical nucleic acid fragments” while the final step of this claim is drawn to identifying, isolating or separating “the fully-matched heterohybrid fragments.” *Id.* The Examiner suggested that this claim does not set forth the relationship between the individual nucleic acid fragments and the fully-matched heterohybrid fragments, and that as a result, it is not clear whether the claims are intended to be limited to a method of identification, isolation or separation of identical nucleic acid fragments or fully-matched heterohybrid fragments. *Id.*

Without acquiescing to the propriety of this rejection, and solely to expedite prosecution of the present application, Applicant has amended claim 23 to read, in relevant part, “identifying, isolating or separating fully-matched heteroduplexes, thereby identifying,

isolating or separating nucleic acid fragments that are identical between the at least two nucleic acid populations.” This amendment, coupled with other amendments to claim 23, clarifies the relationship between identical nucleic acid fragments and fully-matched heteroduplexes (previously referred to as “fully-matched heterohybrid fragments”) defined in claim 23. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection of claim 23.

The Examiner also alleged that claims 23-45 are indefinite due to various recitations that lack antecedent basis. *Id.* at 4-5 (citing MPEP 2173.05). Applicant respectfully traverses.

Without acquiescing to the propriety of this rejection and solely to expedite prosecution of the present application, the claims and recitations at issue have been amended to address the Examiner’s comments. Specifically, in claim 23(g), “the fully-matched heterohybrid fragments” has been replaced with “fully-matched heteroduplexes.” References to nucleic acid populations and amplification products now appear in claim 23(a) and (b) respectively before these terms are referred to subsequently in claim 23(d). The “the” before “adaptor-ligated restriction fragments” has been deleted in claim 23(c). The terms homoduplexes and heteroduplexes appear in claim 23(d). They do not lack antecedent basis in any claims dependent therefrom. Claim 39 specifies that “the hybridization mixture” referred to is that contemplated in claim 23(d), and claim 40 has been deleted. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw these rejections.

In relation to claim 30, the Examiner argued that the phrase “chromosome-specific and sequence-specific fashion,” describing cloning, is indefinite because it is not clear what steps encompass cloning in this manner. *Id.* at 5. Further, the Examiner asserted that this step is not defined in the specification and that it is not clear whether the phrase refers to the use of a specific vector or a specific process to achieve the contemplated cloning. *Id.* Applicant respectfully traverses.

It is important to note that this methodology is defined in the specification, e.g., page 13, lines 17-27. This portion of the specification clearly shows that the use of a particular vector is not required (“the restriction fragments may be cloned into *any* suitable vector ... The vector may be *any* plasmid, phage, virus, cosmid, artificial chromosome ..., *etc.*” (emphasis added)). Moreover, lines 17-27 indicate a specific process by which to clone in a “chromosome-specific and sequence-specific fashion,” namely, homologous recombination. These references in the specification demonstrate that the phrase refers to a specific process,

not a specific vector. *Vitronics Corp. v. Conceptronic, Inc.*, 39 U.S.P.Q.2d 1573, 1582 (Fed. Cir. 1996) quoting *Markman v. Westview Instruments, Inc.*, 34 U.S.P.Q.2d 1321, 1329 (Fed. Cir. 1995) (“The claims must be read in view of the specification of which they are a part.”). Applicant nonetheless has amended claim 30 to specify that the cloning step is performed prior to the amplifying step in this process. Applicant thus respectfully requests that the Examiner reconsider and withdraw this rejection of claim 30.

The Examiner rejected claim 40 as unclear. OA at page 5. Applicant respectfully traverses. Without acquiescing to this rejection, and solely to expedite prosecution of the present application, the Applicant has cancelled claim 40 in this Reply.

The Examiner rejected claim 42 as unclear. *Id.* Applicant respectfully traverses. Without acquiescing to this rejection, and solely to expedite prosecution of the present application, claim 42 has been cancelled in this Reply.

Based on the foregoing amendments and cancellations, Applicant respectfully requests that the Examiner reconsider and withdraw the present rejections of claims 23-45 under 35 U.S.C. § 112, ¶ 2.

### **III. REJECTIONS UNDER 35 U.S.C. § 102(e)**

The Examiner rejected claims 23-45 as anticipated under 35 U.S.C. § 102(e) by Weissman et al. (U.S. Pat. No. 6,287,825) and claims 23-29 and 34-45 as anticipated by Weissman et al. (U.S. Pat. No. 6,150,112). *Id.* at 6-10. Applicant respectfully traverses.

In order to support an anticipation rejection under 35 U.S.C. § 102(e), the Examiner must show that each and every element of the claimed invention is shown identically in a single reference. *In re Bond*, 15 U.S.P.Q.2d 1566, 1567 (Fed. Cir. 1990) citing *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315, 1317 (Fed. Cir. 1988). Further, the elements of the prior art must be arranged as in the claims under review. *Id.*, citing *Lindemann Maschinenfabrik v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 485 (Fed. Cir. 1984). Thus, the references the Examiner asserts as prior art must contain all of the elements contemplated by the present invention in the same order and arrangement as presently claimed. As explained below, the Weissman references do not contain each and every element of the claimed invention as they presently appear. Therefore, the invention as presently claimed is novel and inventive over the cited references.

**A. Claims 23-45 are rejected under 35 U.S.C. § 102(e) as being anticipated by Weissman et al. (U.S. Pat. No. 6,287,825).**

The Examiner argued that claims 23-45 are anticipated under 35 U.S.C. § 102(e) by Weissman et al., U.S. Pat. No. 6,287,825 (“Weissman ‘825”). OA at page 6. Applicant respectfully traverses.

The Examiner asserted that Weissman ‘825 anticipates the present invention because it contemplates (1) digesting nucleic acids from different nucleic acid populations with at least one restriction enzyme, (2) ligating an adaptor sequence to the restriction fragments, (3) amplifying the adaptor-ligated restriction fragments using an adaptor-specific primer, (4) hybridizing the amplification products from the different nucleic acid populations, and (5) identifying, isolating or separating the fully-matched heterohybrid fragments. *Id.* Weissman ‘825 undertakes the steps of the presently claimed process in a fundamentally different way. Thus, Weissman ‘825 does not anticipate the inventive steps defined in the claims of the present application.

As defined in independent claim 23, the present invention includes “(a) digesting separately nucleic acids from a mixture of at least two nucleic acid populations with at least one restriction enzyme; (b) ligating an adaptor sequence to the restriction fragments resulting from the digestion in step (a);” and “(c) amplifying adaptor-ligated restriction fragments generated in step (b) using an adaptor-specific primer.” The use of specific adaptors and adaptor-specific primers in claim 23, produces “amplification products having different ends in respect to each of the at least two nucleic acid populations.” This process leads to blunt-ended homoduplexes and forked-end heteroduplexes after hybridization of the DNA populations. Distinguishing claim 23 from Weissman ‘825, the present invention next teaches “eliminating blunt-ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt-ended double-stranded DNA fragments.” This step is not taught in Weissman ‘825. Next, mismatched heteroduplexes are eliminated by using mismatch repair enzymes, thus identifying, isolating or separating fully-matched heteroduplexes that are identical between the different nucleic acid populations. Weissman ‘825 does not teach eliminating mismatched heterohybrids after specific elimination of blunt-ended homoduplexes. Because Weissman ‘825 does not teach these claimed steps, it does not anticipate claims 23-45 under 35 U.S.C. § 102(e). Applicant thus respectfully requests that the Examiner reconsider and withdraw the present rejection.

The Examiner next asserted that dependent claims 24-28 are anticipated because Weissman '825 contemplates practicing its method with similar DNA types as that contemplated in the present application (i.e., genomic, human genomic, from subjects having common traits). Without acquiescing to the propriety of the Examiner's arguments, because Weissman '825 does not anticipate the methods defined in independent claim 23, dependent claims 24-28 also are not anticipated. The same is true of dependent claims 29, 30, 34, 36 and 39. Applicant thus respectfully requests that the Examiner reconsider and withdraw these 35 U.S.C. § 102(e) rejections.

The Examiner also alleged that Weissman '825 teaches cloning a part of the restriction fragments (e.g., in a vector in a chromosome-specific and sequence-specific fashion) in col. 6. *Id.* at 7. Applicant respectfully traverses.

When cloning is contemplated by the Weissman '825 reference, it occurs after treatment with MutSLH. Col. 6, lines 9-62. Further, cloning is not performed prior to an amplifying step as specified in amended claim 30. *Id.* Because of these fundamental differences, Weissman '825 does not anticipate the present claims. Applicant thus respectfully requests that the Examiner reconsider and withdraw this rejection under 35 U.S.C. § 102(e).

Finally, the Examiner alleged that Weissman '825 teaches digesting perfectly matched DNAs by Exo III and then single-stranded Exo III created strands by binding single-stranded Exo III created strands using a strand-specific matrix. OA at page 8. Col. 1 of Weissman '825 explains the GMS method. The GMS method is disclosed in detail in the present application at pages 6-7. The GMS method does not comprise a step of specifically digesting blunt-ended homoduplexes by Exo III and then eliminating mismatched heterohybrids. Therefore, Weissman '825 does not anticipate the claims of the present invention.

Based on the foregoing discussion, claims 23-45 are not anticipated by Weissman '825. Applicant thus respectfully requests reconsideration and withdrawal of these rejections under 35 U.S.C. § 102(e).

**B. Claims 23-29 and 34-45 are rejected under 35 U.S.C. § 102(e) as being anticipated by Weissman et al. (U.S. Pat. No. 6,150,112).**

The Examiner alleged that claims 23-29 and 34-45 are anticipated under 35 U.S.C. § 102(e) by Weissman et al., U.S. Pat. No. 6,150,112 (“Weissman ‘112”). *Id.* at 8. Applicant respectfully traverses.

The Examiner argued that Weissman ‘112 anticipates the claims of the present invention for essentially the same reasons argued in relation to Weissman ‘825. For the same reasons set forth above in Applicant’s traversal of the Examiner’s rejection of the claims over Weissman ‘825, Weissman ‘112 does not teach the claimed steps of “eliminating blunt-ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt-ended double-stranded DNA fragments” and then “eliminating mismatched heteroduplexes by using mismatch repair enzymes.” Therefore, Weissman ‘112 does not anticipate the claims of the present application.

As with Weissman ‘825, the Examiner alleged that Weissman ‘112 includes digesting perfectly matched DNAs by Exo III and then single-stranded Exo III created strands by binding single-stranded Exo III created strands using a strand specific matrix. *Id.* at 10. As discussed in detail above, the GMS method does not include the steps of digesting blunt-ended homoduplexes by Exo III and then eliminating mismatched heterohybrids. For the foregoing reasons, Weissman ‘112 does not anticipate claims 23-29 and 34-45. Applicant thus respectfully requests that the Examiner reconsider and withdraw the rejection of claims 23-29 and 34-45 under 35 U.S.C. § 102(e).

**IV. REJECTION UNDER 35 U.S.C. § 103**

The Examiner alleged that claims 30-33 are unpatentable under 35 U.S.C. § 103 over Weissman ‘112 in view of Weissman ‘825. *Id.* at 11. Applicant respectfully traverses. Without acquiescing to the propriety of the rejection, and solely to expedite prosecution of the application, claims 31 and 33 have been cancelled. Therefore, any rejection pertaining to these claims is moot.

To maintain a proper rejection under 35 U.S.C. § 103, the Examiner must meet four conditions to establish *prima facie* obviousness. First, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should carry out the claimed process. Second, the Examiner must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the

reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all of the claim limitations. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Examiner must show that these references contained a suggestion, teaching, or motivation to combine the prior art references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999).

Without addressing the propriety of the Examiner's statements regarding the specific teachings of the Weissman '825 and '112 patents, Applicant respectfully submits that these references, singly or in combination, cannot support a rejection of the present claims under 35 U.S.C. § 103. Specifically, as discussed in detail above, neither of the Weissman patents teaches nor suggests the steps of "eliminating blunt ended homoduplexes from heteroduplexes having forked ends by digesting the homoduplexes with an enzyme that specifically digests blunt-ended double-stranded DNA fragments" and then "eliminating mismatched heteroduplexes by using mismatch repair enzymes." Because neither Weissman '825 nor Weissman '112 teaches or suggests these steps, their combination does not support an obviousness rejection under 35 U.S.C. § 103. Applicant therefore respectfully requests reconsideration and withdrawal of this rejection.

#### **V. ALLEGED PRIOR ART**

The Examiner listed Grant et al., U.S. Pat. No. 6,524,794 ("Grant '794") as prior art not relied upon. Applicant respectfully traverses.

Grant '794 was filed 29 October 1999, over six months after the present application's priority date. Grant '794 thus does not constitute prior art to the present application.




**CONCLUSION**

Applicant has properly and fully addressed each of the Examiner's grounds for rejection. Applicant submits that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited.

If there are any further fees due in connection with the filing of the present reply, please charge the fees to undersigned's Deposit Account No. 50-1067. If a fee is required for an extension of time not accounted for, such an extension is requested and the fee should be charged to undersigned's deposit account.

Respectfully submitted,

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Don J. Pelto  
Reg. No. 33, 754

Preston Gates Ellis & Rouvelas Meeds LLP  
1735 New York Avenue NW, Suite 500  
Washington, DC 20006  
Telephone: (202) 628-1700  
Facsimile: (202) 331-1024